TRANSMITTAL LETTER TO THE UNITED STATES ATTORNEY'S DOCKET NUMBER 50733

DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371 U S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09051	**15 September 2000**	**16 September 1999**

TITLE OF INVENTION: METHOD FOR THE PRODUCTION OF POLYVINYLPYRROLIDONE-IODINE IN A AQUEOUS SOLUTION

APPLICANT(S) FOR DO/EO/US
Helmut WITTELER, Axel SANNER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C 371

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C 371

3. /X/ This express request to begin national examination procedures (35 U.S C 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U S.C. 371(b) and PCT Articles 22 and 39(1)

4. /x / A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date

5. /X/ A copy of the International Application as filed (35 U.S C 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b / / has been transmitted by the International Bureau
   c / / is not required, as the application was filed in the United States Receiving Office (RO/US0)

6. /X/ A translation of the International Application into English (35 U.S C. 371(c)(2))

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U S C. 371(c)(3))

   a / / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau
   c./ / have not been made; however, the time limit for making such amendments has NOT expired
   d / / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U S.C. 371(c)(3))

9. / / An oath or declaration of the inventor(s)(35 U.S C 171(c)(4))

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U S C 371(c)(5)).

Items 11. to 16 below concern other document(s) or information included:

11 / / An Information Disclosure Statement under 37 CFR 1 97 and 1.98.

12 / x/ An assignment document for recording A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included

13./x / A FIRST preliminary amendment
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification

15./ / A change of power of attorney and/or address letter

16./x / Other items or information
International Search Report
International Preliminary Examination Report

10/070758 .031202

10/070758

JC10 Rec'd PCT/PTO 12 MAR 2002

U S. Appln No (If Known)	INTERNATIONAL APPLN. NO. PCT/EP00/09051	ATTORNEY'S DOCKET NO. 50733

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.. ... .$890 00	**890.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $710 00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..... ..... $740 00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1 445(a)(2)) paid to USPTO .....$ 1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1 482) and all claims satisfied pro -visions of PCT Article 33(2)-(4)..... ... .$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890 00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1 492(e))		

Claims	Number Filed	Number Extra	Rate	
Total Claims	12	-20	X$18	
Indep.Claims	1	-3	X$84	
Multiple dependent claim(s)(if applicable)			+280	
TOTAL OF ABOVE CALCULATION			= **890.**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1 9, 1.27, 1.28).				
SUBTOTAL			= 890	
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)).		+		
TOTAL NATIONAL FEE			= **890 .**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3 28, 3 31) $40 00 per property		=	40	
TOTAL FEES ENCLOSED			= **$ 930.00**	
		Amount to be refunded	$	
		Charged	$	

a./X/ A check in the amount of $ 930.00 to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____in the amount of $_____ to cover the above fees A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **11-0345**. A duplicate copy of this sheetis enclosed

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1 137(a) or (b) must be filed and granted to restore the application to pending status.

Herbert B Keil

SIGNATURE

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SEND ALL CORRESPONDENCE TO:
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of
WITTELER et al.

BOX PCT

International Application
PCT/EP 00/09051

Filed: September 15, 2000

For: PREPARATION FOR PREPARING POLYVINYLPYRROLIDONE-IODINE IN AQUEOUS SOLUTION

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claims as shown on the attached sheets.

REMARKS

The claims have been amended to eliminate multiple dependency and to place them in better form for U.S. filing. No new matter is included.

A clean copy of the claims is attached.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF

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CLEAN VERSION OF AMENDED CLAIMS - OZ 50733

3. A process as claimed in claim 1, wherein the mixing is carried out in the presence of a reducing agent.

4. A process as claimed in claim 1, wherein the reducing agent is selected from formic acid, oxalic acid, the esters and salts of formic and oxalic acids, and the amides of carbonic acid, of formic acid and of oxalic acid.

5. A process as claimed in claim 1, wherein the polyvinylpyrrolidone solution and, where appropriate, at least part of the reducing agent are mixed, the mixture is heated where appropriate, and then iodine is added.

6. A process as claimed in claim 1, wherein a polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of > 27 and a polyvinylpyrrolidone content of > 35% by weight is employed.

7. A process as claimed in claim 1, wherein the polyvinylpyrrolidone-iodine present in the solution has an available iodine content of at least 4% by weight.

8. A polyvinylpyrrolidone-iodine solution obtainable by a process as claimed in claim 1.

10. The use of an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or of solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution for producing compositions for disinfection, antisepsis or for wound treatment.

12. An antiseptic composition comprising an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution.

MARKED VERSION OF AMENDED CLAIMS - OZ 50733

3. A process as claimed in claim 1 [or 2], wherein the mixing is carried out in the presence of a reducing agent.

4. A process as claimed in claim 1 [any of the preceding claims], wherein the reducing agent is selected from formic acid, oxalic acid, the esters and salts of formic and oxalic acids, and the amides of carbonic acid, of formic acid and of oxalic acid.

5. A process as claimed in claim 1 [any of the preceding claims], wherein the polyvinylpyrrolidone solution and, where appropriate, at least part of the reducing agent are mixed, the mixture is heated where appropriate, and then iodine is added.

6. A process as claimed in claim 1 [any of the preceding claims], wherein a polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of > 27 and a polyvinylpyrrolidone content of > 35% by weight is employed.

7. A process as claimed in claim 1 [any of the preceding claims], wherein the polyvinylpyrrolidone-iodine present in the solution has an available iodine content of at least 4% by weight.

8. A polyvinylpyrrolidone-iodine solution obtainable by a process as claimed in claim 1 [any of claims 1 to 7].

10. The use of an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or of solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution [as defined in claim 9] for producing compositions for disinfection, antisepsis or for wound treatment.

12. An antiseptic composition comprising an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution [as defined in claim 9].

CLAIMS AS FILED - OZ 50733

1. A process for preparing polyvinylpyrrolidone-iodine in aqueous solution, where an aqueous polyvinylpyrrolidone solution and at least 4.0% by weight of elemental iodine, based on the polyvinylpyrrolidone calculated as solid, are mixed, wherein at the time of mixing the concentration c of the aqueous polyvinylpyrrolidone, based on the total amount of polyvinylpyrrolidone and water, and the K value of polyvinylpyrrolidone obeys the following relation:

$$c > 100 \times [0.1 + 8 : (K + 5)]$$

where c is stated in % by weight, and the Fikentscher K value is in the range from 10 to 100.

2. A process as claimed in claim 1, wherein the mixture is heated at a temperature in the range from 50 to 110°C for a period of from 30 minutes to 15 hours.

3. A process as claimed in claim 1, wherein the mixing is carried out in the presence of a reducing agent.

4. A process as claimed in claim 1, wherein the reducing agent is selected from formic acid, oxalic acid, the esters and salts of formic and oxalic acids, and the amides of carbonic acid, of formic acid and of oxalic acid.

5. A process as claimed in claim 1, wherein the polyvinylpyrrolidone solution and, where appropriate, at least part of the reducing agent are mixed, the mixture is heated where appropriate, and then iodine is added.

6. A process as claimed in claim 1, wherein a polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of > 27 and a polyvinylpyrrolidone content of > 35% by weight is employed.

7. A process as claimed in claim 1, wherein the polyvinylpyrrolidone-iodine present in the solution has an available iodine content of at least 4% by weight.

8. A polyvinylpyrrolidone-iodine solution obtainable by a process as claimed in claim 1.

9. A solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8.

10. The use of an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or of solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution for producing compositions for disinfection, antisepsis or for wound treatment.

11. The use as claimed in claim 10 for producing wound coverings.

12. An antiseptic composition comprising an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution.

Process for preparing polyvinylpyrrolidone-iodine in aqueous solution

The present invention relates to a process for preparing polyvinylpyrrolidone-iodine (PVP-iodine) in aqueous solution. Polyvinylpyrrolidone-iodine is the product of the reaction of polyvinylpyrrolidone (PVP) with elemental iodine, which is increasingly used because of its germicidal, bactericidal, fungicidal and disinfectant properties.

Processes for preparing PVP-iodine are known in principle. Preparation ordinarily takes place by mixing polyvinylpyrrolidone as solid or solution with iodine or iodine compounds. However, problems arise in the preparation of PVP-iodine with good stability together with good availability of the iodine content.

One measure of the stability of a PVP-iodine is the distribution coefficient (DC) of the iodine between an aqueous PVP-iodine solution and heptane. This is determined according to US-A-3,028,300 by vigorously shaking an iodine solution with an available iodine content of 1.0% with heptane at 25°C for one minute and is, if the binding between polyvinylpyrrolidone and iodine is sufficiently strong, about 200 or above. Another measure of the stability, in particular the storage stability, of PVP-iodine is determination of the iodine loss, i.e. the percentage decrease in available iodine, on heating for a defined period.

An important characteristic variable for the stability of PVP-iodine is the iodine:iodide ratio. When the iodine:iodide ratio is about 2:1 the linkage of PVP and iodine is ordinarily so strong that an iodine odor is no longer perceptible and a moist potassium iodide/starch paper introduced into the gas space above the sample does not develop a color.

A number of publications, e.g. DE-B 10 37 075, US-A 2,900,305, US-A 2,826,532, US-A 3,028,300, US-A 3,898,326 and DE-B 24 39 197, describe procedures intended to provide PVP-iodine with improved properties. However, the aforementioned processes either lead to PVP-iodine complexes with unsatisfactory stability or require for the formation of a sufficiently strong binding between PVP and iodine a heat treatment, i.e. the PVP-iodine which has been formed is subsequently heated at temperatures of from 70 to 90°C ordinarily for a period of more than 10 hours, in most cases in the range from 20 to 64 hours. To achieve acceptable preparation times, the heat treatment must be

carried out at comparatively high temperatures, i.e. above 70°C. The heat treatment of PVP-iodine in powder form is technically very elaborate because the powder is very prone to aggregation at these temperatures. If, on the other hand, the heat treatment is carried out in aqueous solution, there is usually observed to be a large loss of iodine through formation of a sediment and/or through sublimation at the necessary temperatures.

DE-A 25 40 170 describes the use of a polyvinylpyrrolidone and alkali metal iodides as iodine ion-providing compound, which lead to PVP-iodine of satisfactory stability without long heat treatment. The resulting PVP-iodine solutions cannot, however, be used for pharmaceutical products because of their ash content.

EP-A 027 613 describes a process for preparing PVP-iodine in which PVP, elemental iodine and a compound promoting iodide formation are reacted in aqueous solution. The complete reaction time, i.e. the time referred to as reaction time and the time required for the heat treatment, is in the range from 7 to 32 hours, despite the use of the compound promoting iodide formation, and the complete reaction time required in this process to achieve an iodine loss of less than about 7% is at least 14 hours. The PVP solutions employed are those with a concentration of 50% by weight and a K value of 13, a concentration of 40% by weight and a K value of 17 and a concentration of 30% by weight and a K value of 32.

It is an object of the present invention to provide a process which makes it possible easily and quickly to prepare PVP-iodine starting from elemental iodine. It is additionally intended to provide PVP-iodine which has an improved stability, in particular improved storage stability.

We have found that this object is achieved by a process in which there is conversion of the polyvinylpyrrolidone in aqueous solution with a high concentration and, preferably, a high K value using elemental iodine into polyvinylpyrrolidone-iodine. It was surprising in this connection that on use of polyvinylpyrrolidone solutions in the concentrations of the invention the reaction times are markedly shortened and the PVP-iodine which is formed shows a markedly reduced iodine loss. It was particularly surprising that the PVP solutions and PVP-iodine solutions even with high concentrations and high K values show a comparatively low viscosity and no or only slight increases in viscosity during the process, so that it is ensured that the process is easy to carry out.

The present invention therefore relates to a process for preparing polyvinylpyrrolidone-iodine in aqueous solution, where an aqueous polyvinylpyrrolidone solution and at least 4.0% by weight of elemental iodine, based on the polyvinylpyrrolidone calculated as solid, are mixed, wherein at the time of mixing the concentration c of the aqueous polyvinylpyrrolidone, based on the total amount of polyvinylpyrrolidone and water, and the K value of polyvinylpyrrolidone obeys the following relation:

$$c > 100 \times [0.1 + 8 : (K + 5)]$$

where c is stated in % by weight, and the Fikentscher K value is in the range from 10 to 100. The concentration c therefore relates only to the ratio of polyvinylpyrrolidone to water.

The polyvinylpyrrolidone-iodine solutions prepared by the process of the invention, and the solid PVP-iodine obtainable therefrom by removing the water and other volatile constituents, preferably have an iodine:iodide ratio of about 2:1 and a distribution coefficient (DC), determined as disclosed in US-A 3,028,300, in the range from 190 to 250. The PVP-iodine obtainable according to the invention preferably has an iodine loss of < 6%, preferably < 5% and particularly preferably < 4%, determined on aqueous solutions with an available iodine content of 1.0% after storage at 80°C for 15 hours.

The concentration c in the relation stated above represents a minimum concentration, which depends on the K value of polyvinylpyrrolidone employed, of the solutions to be used according to the invention. It is preferred for the maximum concentration c of the polyvinylpyrrolidone solution during the process of the invention to be below 90% by weight, preferably below 85% by weight and particularly preferably below 80% by weight.

The concentration c of the aqueous polyvinylpyrrolidone, based on the total amount of polyvinylpyrrolidone and water, and the K value of the polyvinylpyrrolidone at the time of mixing preferably obeys the relation $c > 100 \times [0.1 + 8 : (K + 2)]$.

The Fikentscher K value is a measure of the molecular weight of the polyvinylpyrrolidone and is determined as described by H. Fikentscher, Cellulose-Chemie, 13, 58-64 and 71-74 (1932) as 1% by weight solution in water.

Polyvinylpyrrolidones suitable for the process of the invention have K values in the range from 10 to 100, preferably 20 to 50 and particularly preferably 25 to 50, e.g. about 30 or about 40. However, it is also possible and advantageous for polyvinylpyrrolidones with higher K values to be processed, e.g. polyvinylpyrrolidones with K values of about 70 or about 85, in the process of the invention.

Polyvinylpyrrolidones with K values in the range from 10 to 20 are preferably employed in a concentration c in the range from 65 to 90% by weight, particularly preferably 70 to 85% by weight, in the process of the invention. Polyvinylpyrrolidones with K values in the range from > 20 to 27 are preferably employed in a concentration c of from 43 to 80% by weight, particularly preferably 45 to 70% by weight, in the process of the invention. It is preferred to employ in the process of the invention a polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of > 27 and a polyvinylpyrrolidone content of > 35% by weight. Polyvinylpyrrolidones with a K value in the range from 28 to 50, e.g. about 30 or about 40, are preferably employed in a concentration c of 36 to 75% by weight, particularly preferably 42 to 65% by weight and very particularly preferably 45 to 55% by weight, e.g. about 45% by weight. Polyvinylpyrrolidones with a K value in the range from > 50 to 100, e.g. about 60, about 70 or about 90, are preferably employed in a concentration c of from 18 to 50% by weight, particularly preferably 19 to 40% by weight and very particularly preferably 20 to 35% by weight, e.g. about 25% by weight.

The polyvinylpyrrolidone employed in the process of the invention can in principle be obtained in any way. Polyvinylpyrrolidone suitable for the process of the invention can be prepared, for example, by polymerization in an organic solvent such as isopropanol or toluene, using free-radical formers, especially organic peroxy compounds, e.g. dialkyl peroxides, or azo compounds, e.g. AIBN, and subsequently be subjected where appropriate to an after-treatment, e.g. a steam distillation. The polyvinylpyrrolidone can, for example, also be prepared by free-radical polymerization in water, where appropriate mixed with organic solvents in the presence of water-soluble free-radical formers, e.g. hydrogen peroxide or sodium peroxodisulfate. A number of process for preparing polyvinylpyrrolidone are known to the skilled worker and are described, for example in Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme-Verlag, Stuttgart.

Also suitable for the process of the invention are polyvinylpyrrolidones subjected to a hydrogenation process after the polymerization. This involves hydrogenation of the polyvinylpyrrolidone by conventional known processes. A hydrogenation with hydrogen is described, for example, in US-A 2,914,516. Likewise suitable are polyvinylpyrrolidones which have been treated with complex hydrides, which are described, for example, in EP-A 027 613.

The polyvinylpyrrolidones described in DE-B 28 18 767, EP-A 027 613, the processes for preparing them and suitable reactants and reaction conditions can also be employed analogously for preparing the highly concentrated polyvinylpyrrolidone solution employed according to the invention. Express reference is hereby made to these two publications.

Further sources of iodine which can be employed besides elemental iodine are iodines or other iodine-providing compounds, employing, based on the polyvinylpyrrolidone calculated as solid, at least 4.0% by weight, in particular at least 6.0% by weight and particularly preferably at least 8.0% by weight, of elemental iodine. The elemental iodine will ordinarily be employed in an amount in the range from 5 to 35% by weight, preferably 10 to 30% by weight and in particular 15 to 25% by weight, e.g. about 20% by weight. Examples of compounds suitable as further sources of iodine are hydrogen iodide, alkali metal and alkaline earth metal iodides, especially alkali metal iodides, e.g. sodium iodide and potassium iodide, polyiodides, in particular alkali metal polyiodides, ammonium iodides, in particular tetraalkylammonium iodides, e.g. tetramethylammonium iodide, phosphorus triiodide, and organic acid iodides, e.g. acetyl iodide. It is preferred for at least 50%, in particular at least 75% and particularly preferably at least 90%, of the iodine present in the polyvinylpyrrolidone-iodine to be employed in the form of elemental iodine. In a preferred embodiment of the process of the invention, elemental iodine is employed as the exclusive source of iodine.

In the process of the invention it is possible for the reactants, i.e. iodine, polyvinylpyrrolidone and, where appropriate, reducing agent and, where appropriate, auxiliaries to be mixed, independently of one another, undiluted or in suspension or solution. The mixing of the reactants to form the PVP-iodine is carried out at a concentration c as defined above.

It is possible, for example, in the process of the invention for the iodine and, where appropriate, further sources of iodine to be introduced into a solvent, preferably water, and be heated where appropriate. Subsequently, the polyvinylpyrrolidone, preferably as aqueous solution, is added and the reaction mixture is mixed. The mixing of the reactants can take place at the same temperature as the addition of the polyvinylpyrrolidone or at another, preferably a higher, temperature.

In the process of the invention, preferably the polyvinylpyrrolidone is introduced as aqueous solution and heated where appropriate. Subsequently, iodine and, where appropriate, further sources of iodine are added, and the reaction mixture is mixed. The addition of the iodine and, where appropriate, the further sources of iodine can take place all at once, in a plurality of portions or continuously. The mixing can take place at the same temperature as the addition of the iodine and, where appropriate, of the further sources of iodine or at another, preferably a higher, temperature.

The iodine and, where appropriate, the further sources of iodine can be added undiluted or as suspension or solution, e.g. in water or organic solvents.

It is preferred for at least the mixing of the reactants, in particular the polyvinylpyrrolidone and the iodine, to be carried out at a temperature above 50°C.

When the process of the invention is carried out in the presence of a reducing agent, the addition can take place in whole or in part by premixing the reducing agent and PVP and/or by adding reducing agent to the initial charge and/or by adding reducing agent during the mixing.

For the purposes of this invention, mixing means a blending or homogenization intended to increase the contact of the components to be mixed, also referred to as reactants herein, and thus make a uniform and/or rapid formation of the desired product possible. It is possible by the mixing to generate a mixture which is as homogeneous as possible and/or to initiate or speed up a chemical reaction.

Methods capable of bringing about mixing are, for example, stirring, shaking, injection of gases or liquids and exposure to ultrasound.

Suitable processes and devices bringing about mixing are known to the skilled worker. Examples of suitable mixing devices are those also employed for mixing in plastics technology. Suitable devices are described, for example, in "Mischen beim Herstellen und Verarbeiten von Kunststoffen", H. Pahl, VDI-Verlag 1986. Suitable mixing apparatuses are, for example, stirred vessels, dynamic and static mixers, single-shaft stirrers, for example stirrers with stripper mechanisms, especially paste mixers, multishaft stirrers especially PDSM mixers, solids mixers, and mixer/kneader reactors (e.g. ORP, CRP, AP, DTP from List and Reaktotherm from Krauss-Maffei), x trough mixers and internal mixers, extruders, e.g. the ZKS models from Werner & Pfleiderer, and rotor-stator systems, e.g. Dispax from Ika. Suitable extruders are, for example, single-screw machines, intermeshing screw machines or else multiscrew extruders, especially twin screw extruders, e.g. corotating or counterrotating twin screw extruders. Heatable mixing devices are preferably used.

The process of the invention is preferably carried out at a temperature in the range from 10 to 110°C, preferably in the range from 20 to 105°C. It is preferred for the reaction time in the process of the invention to be from 20 minutes to 20 hours, preferably 30 minutes to 12 hours and particularly preferably 1 hour to 6.5 hours. Within the meaning of this invention, the reaction time means the time between the first contact of a source of iodine with polyvinylpyrrolidone in aqueous solution until a stable PVP-iodine solution is present. A stable PVP-iodine solution means for the purposes of this invention preferably a PVP-iodine solution which shows an iodine loss within the aforementioned limits determined by the aforemented methods.

In the process of the invention it is preferred that the mixture is heated at a temperature in the range from 50 to 110°C, in particular 70 to 105°C and very particularly preferably in the range from 85 to 100°C for a period of from 30 minutes to 15 hours, in particular 60 minutes to 12 hours and particularly preferably 60 minutes to 6.5 hours.

The mixing can also be carried out in the presence of a reducing agent. Suitable reducing agents are, in particular, those able to promote the formation of iodide from elemental iodine. Particularly suitable compounds are those which after the reaction with iodine form exclusively volatile substances such as, for example, carbon dioxide or nitrogen in addition to the iodide and, where appropriate, water. The reducing agent is preferably selected from formic acid, oxalic acid, the esters and

salts of formic and oxalic acids, and the amides of carbonic acid, of formic acid and of oxalic acid.

Examples of particularly suitable reducing agents are ammonium carbonate, ammonium bicarbonate, ammonium carbamate, urea, ammonium formate, formamide, ammonium oxalate, oxamic acid and oxamide. Oxalic acid and formic acid, and their amides and ammonium salts, are particularly preferred. Oxalic acid and formic acid are very particularly preferred and, in the reaction with iodine, form only carbon dioxide in addition to hydrogen iodide.

The amount of reducing agent is ordinarily such that, when reaction is complete, 1/5 to 2/5, preferably about 1/3, of the added iodine is converted into iodide. The amount is therefore between 2 and 30% by weight, preferably 4 and 22% by weight, calculated according to the iodine employed, depending on the nature of the addition.

It is preferred for the polyvinylpyrrolidone-iodine solutions prepared by the process of the invention to have an available iodine content, i.e. iodine which can be titrated with thiosulfate, in the range from 2 to 40% by weight, preferably 4 to 30% by weight and particularly preferably 7.5 to 15% by weight, based on the total weight of PVP-idine, calculated as solid. The PVP-iodine solutions obtained with this process can be diluted or concentrated virtually as desired, e.g. as far as solid PVP-iodine.

The process of the invention is to be explained in more detail hereinafter by means of some embodiments:

The process of the invention can be carried out, for example, in such a way that iodine and, where appropriate, further sources of iodine are added to water and, where appropriate reducing agent, and subsequently PVP solution is added with stirring. It is preferred for the aqueous iodine-containing reaction mixture after the addition of the iodine or the sources of iodine to be vigorously mixed, e.g. for 10 minutes to 120 minutes, before the PVP solution is added. It is preferred for the reaction mixture to be heated after the addition of the PVP solution to 70 to 100°C, e.g. about 90°C, over the course of 10 minutes to 2 hours, e.g. about 1 hour, and subsequently be mixed further for 2 to 10 hours.

In a preferred embodiment of the process of the invention, the polyvinylpyrrolidone solution and, where appropriate, reducing agent are heated to a temperature in the range from 50 to 110°C, preferably 70 to 105°C and particularly preferably to a temperature of about 85°C or about 100°C, at this temperature elemental iodine and, where appropriate, further sources of iodine are added, and the reactants are mixed for 2 to 12 hours, preferably 2.5 to 10 hours and particularly preferably 3 to 6.5 hours. The addition of the elemental iodine and, where appropriate, of the further sources of iodine can take place in one portion, in 2 to 15 portions, for example 5 or 10 portions, or continuously. If the iodine or the sources of iodine are added in a plurality of portions or continuously, the addition preferably takes place over a period of from 20 to 90, preferably 30 to 70 and particularly preferably 40 to 60, minutes.

In a particularly preferred embodiment of the process of the invention, a PVP solution of a polyvinylpyrrolidone with a K value of > 27 and a concentration c of about 45% by weight is mixed with a reducing agent, preferably formic acid, and then elemental iodine is added in a plurality of portions, preferably about 10 identical portions, the interval between the individual portions being a few minutes, preferably about 5 to 10 minutes. The iodine can be added in the region of room temperature, e.g. about 25°C, or to the initial charge which has been heated to a temperature in the range from 40 to 100°C, e.g. about 50°C or about 85°C. After the addition is complete, the region mixture is mixed at a temperature in the range from 70 to 100°C, e.g. about 85°C, for a further 2 to 6 hours. The reaction mixture can subsequently only be diluted by addition of water, for example to a solids content in the range from 5 to 40% by weight, such as about 20% by weight or about 30% by weight.

The polyvinylpyrrolidone-iodine solutions obtainable by this process preferably have an available iodine content of at least 4% by weight, based on the polyvinylpyrrolidone-iodine, calculated as solid.

The PVP-iodine solutions prepared according to the invention can be formulated directly in a conventional way, e.g. with addition of further auxiliaries, for example surfactants, to the final products intended for the user. These solutions generally have a total solids concentration of from 10 to 50% by weight.

The present invention further relates to a polyvinylpyrrolidone-iodine solution obtainable by a process as described above. The PVP-iodine solutions of the invention preferably comprise a

polyvinylpyrrolidone with a K value of from 25 to 90 and, in particular, 25 to 35 and a PVP-iodine solids content in the range from 25 to 55% by weight, in particular 30 to 50% by weight. The PVP-iodine solutions of the invention advantageously show an iodine loss of less than 4%, determined after 15 h at 80°C, and a free iodine (volatile iodine) content of less than 2 ppm.

The present invention further relates to a solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution as defined above.

The present invention further relates to the use of an aqueous polyvinylpyrrolidone-iodine solution or of solid polyvinylpyrrolidone-iodine as defined above for producing compositions for disinfection, antisepsis or for wound treatment, and for producing wound coverings.

The present invention further relates to an antiseptic composition comprising an aqueous polyvinylpyrrolidone-iodine solution or solid polyvinylpyrrolidone-iodine as described above.

A further advantage of the polyvinylpyrrolidone-iodine solution obtainable according to the invention is that it can be employed directly as solution and it is unnecessary first to isolate the PVP-iodine from the aqueous solution since the PVP-iodine solutions prepared according to the invention have advantageously high concentrations. It is therefore not ordinarily necessary for them to undergo elaborate concentration; on the contrary, they can be formulated directly, where appropriate after dilution, to PVP-iodine solutions ready for use. The high concentration of the PVP-iodine solutions prepared according to the invention is also advantageous if the intention is to prepare therefrom, by removing the water and other volatile constituents, solid polyvinylpyrrolidone-iodine, for example polyvinylpyrrolidone-iodine powder or granules, since fewer volatile constituents, in particular water, need to be removed. The novel polyvinylpyrrolidone-iodine solutions obtainable by this process surprisingly have, despite the reduced reaction time, a greater stability than conventional solutions, as is evident in particular from an iodine loss of < 5%.

Solid PVP-iodine can, if desired, be obtained from the PVP-iodine solutions obtained according to the invention for example by precipitating the PVP-iodine from the solution and, where appropriate, subsequently filtering off, or by a drying process,

for example by freeze-drying, drum drying, spray drying or spray granulation.

The following examples illustrate the invention without restricting it. The K values were determined as described by H. Fikentscher (see above). The iodine loss (IL) was determined by storing an aqueous PVP-iodine solution with an available iodine content of 1% at a temperature of 80°C for 15 hours. The distribution coefficient (DC) was determined as described in US-A 3,028,300 by vigorously shaking 1.0 ml of an aqueous PVP-iodine solution with an available iodine content of 1.0% with 25 ml of heptane in a closed glass flask in a thermostated heating bath at 25°C for 1 minute. After standing for some minutes, the two phases were separated and the iodine content in the aqueous phase was determined by titration with sodium thiosulfate and the iodine content in the heptane phase was determined by spectrophotometry. The calculation took place in accordance with the following equation:

$$DC = \frac{\text{mg of iodine in } H_2O \text{ phase}}{\text{mg of iodine in heptane}} \times \frac{\text{ml of heptane (25)}}{\text{ml } H_2O \text{ phase (1)}}$$

Examples

The analytical data of the comparative example (CE1) and the examples according to the invention (E2 to E9) are compiled in table 1.

Comparative example 1

1 140 g of a 17.5% by weight polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of 30 and 1.86 g of formic acid were introduced into a stirred reactor. Then, while stirring, 35 g of elemental iodine were added in 10 equal portions at intervals of about 5 minutes. The reaction mixture was then heated to 70°C while stirring and stirred at this temperature for a further 20 hours. The reaction mixture had an inconsistent viscosity because of agglomerates.

Example 2

733 g of polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of 30 and a concentration c of 45% by weight and 3.72 g of formic acid were introduced into a stirred vessel and heated to 100°C. Then, while stirring, 70 g of elemental iodine

were added in 10 equal portions at intervals of about 5 minutes. This was followed by stirring at this temperature for a further 10 hours. The reaction mixture was then diluted with water to a solids content of 30.0% by weight.

Example 3

1.369 kg of polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of 30 and a concentration c of 45% by weight and 6.95 g of formic acid were introduced into a stirred vessel and heated to 85°C while stirring. Then, while stirring, 131 g of elemental iodine were added in 10 equal portions at intervals of about 5 minutes. This was followed by stirring the reaction mixture at 85°C for 7.5 hours and then diluting with water to a solids content of 30% by weight.

Example 4

733 g of polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of 30 and a concentration c of 45% by weight and 3.72 g of formic acid were introduced into a stirred vessel and heated to 85°C. Then, while stirring, 70 g of elemental iodine were added in 10 equal portions at intervals of about 5 minutes. This was followed by stirring at this temperature for a further 6 hours. The reaction mixture was then diluted with water to a solids content of 30.0% by weight.

Example 5

Example 5 was carried out in analogy to example 4 in a pilot plant with a scaleup factor of 130.

Example 6

Example 6 was carried out in analogy to example 4, but with stirring at 90°C for 6 hours after completion of the addition of iodine.

Example 7

733 g of polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of 30 and a concentration c of 45% by weight and 3.72 g of formic acid were introduced into a stirred vessel and heated to 50°C. Then, while stirring, 70 g of elemental iodine were added in 10 equal portions at intervals of about 5 minutes. This was followed by rapidly heating the reaction mixture to 85°C

while stirring, stirring at 85°C for a further 6 hours and then diluting with water to a solids content of 30% by weight.

Example 8

Example 8 was carried out in analogy to example 7, but the iodine was added at 25°C, and stirring at 85°C was for only 4 hours.

Example 9

Example 9 was carried out in analogy to example 8, but stirring at 85°C was for only 3 hours.

No formation of a sediment was observed in any of examples E2 to E9 according to the invention. Examples E2 to E9 according to the invention all had distribution coefficients DC in the region of about 200 or above and met the specifications for use in pharmaceuticals.

Table 1:

	PVP solution			Red. agent[1] [g]	Iodine [kg]	Reaction temperature[2] [°C]	Reaction time [hours]	PVP-iodine solution			
	Amount [kg]	c [% by wt]	K value					SC before dilution[3]	SC after dilution[3]	Avail. iodine[4] [% by wt]	Iodine loss[5] [% by wt]
CE1	1.140	17.5	30	1.86	0.035	25 / 70	21	19,6	-	9.68	4.38
E2	0.733	45	30	3.72	0.070	100	11	ca. 50	30.0	10.0	4.8
E3	1.369	45	30	6.95	0.131	100	8.5	ca. 50	30.0	10.9	4.6
E4	0.733	45	30	3.72	0.070	85	7	ca. 50	30.0	11.9	1.7
E5[6]	178.1	45	30	903	17.03	85	7	ca. 50	29.5	10.8	3.6
E6	0.733	45	30	3.72	0.070	85 / 90	7	ca. 50	30.2	11.4	2.6
E7	0.733	45	30	3.72	0.070	50 / 85	7	ca. 50	29.9	11.6	2.6
E8	0.733	45	30	3.72	0.070	25 / 85	5	ca. 50	29.9	12.25	3.3
E9	0.733	45	30	3.72	0.070	25 / 85	4	ca. 50	30.3	11.86	3.4

1) Formic acid, 100%

2) Where two figures are stated, the first figure relates to the temperature during addition of iodine

3) SC stands for solids content in % by weight

4) Determined by titration with thiosulfate

5) Determined after heating a 1% strength solution at 80°C for 15 hours

6) Pilot plant test

We claim:

1. A process for preparing polyvinylpyrrolidone-iodine in aqueous solution, where an aqueous polyvinylpyrrolidone solution and at least 4.0% by weight of elemental iodine, based on the polyvinylpyrrolidone calculated as solid, are mixed, wherein at the time of mixing the concentration c of the aqueous polyvinylpyrrolidone, based on the total amount of polyvinylpyrrolidone and water, and the K value of polyvinylpyrrolidone obeys the following relation:

$$c > 100 \times [0.1 + 8 : (K + 5)]$$

where c is stated in % by weight, and the Fikentscher K value is in the range from 10 to 100.

2. A process as claimed in claim 1, wherein the mixture is heated at a temperature in the range from 50 to 110°C for a period of from 30 minutes to 15 hours.

3. A process as claimed in claim 1 or 2, wherein the mixing is carried out in the presence of a reducing agent.

4. A process as claimed in any of the preceding claims, wherein the reducing agent is selected from formic acid, oxalic acid, the esters and salts of formic and oxalic acids, and the amides of carbonic acid, of formic acid and of oxalic acid.

5. A process as claimed in any of the preceding claims, wherein the polyvinylpyrrolidone solution and, where appropriate, at least part of the reducing agent are mixed, the mixture is heated where appropriate, and then iodine is added.

6. A process as claimed in any of the preceding claims, wherein a polyvinylpyrrolidone solution of a polyvinylpyrrolidone with a K value of > 27 and a polyvinylpyrrolidone content of > 35% by weight is employed.

7. A process as claimed in any of the preceding claims, wherein the polyvinylpyrrolidone-iodine present in the solution has an available iodine content of at least 4% by weight.

8. A polyvinylpyrrolidone-iodine solution obtainable by a process as claimed in any of claims 1 to 7.

9. A solid polyvinylpyrrolidone-iodine obtainable by removing the water and other volatile constituents from an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8.

10. The use of an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or of solid polyvinylpyrrolidone-iodine as defined in claim 9 for producing compositions for disinfection, antisepsis or for wound treatment.

11. The use as claimed in claim 10 for producing wound coverings.

12. An antiseptic composition comprising an aqueous polyvinylpyrrolidone-iodine solution as defined in claim 8 or solid polyvinylpyrrolidone-iodine as defined in claim 9.

Abstract

The present invention relates to a process for preparing polyvinylpyrrolidone-iodine in aqueous solution, where an aqueous polyvinylpyrrolidone solution in at least 4.0% by weight of elemental iodine, based on the polyvinylpyrrolidone calculated as solid, are mixed, wherein at the time of mixing the concentration c of the aqueous polyvinylpyrrolidone, based on the total amount of polyvinylpyrrolidone and water, and the K value of polyvinylpyrrolidone obeys the following relation:

$$c > 100 \times [0.1 + 8 : (K + 5)]$$

where c is stated in % by weight, and the Fikentscher K value is in the range from 10 to 100, to the polyvinylpyrrolidone-iodine solutions obtainable by this process, to solid polyvinylpyrrolidone-iodine which can be obtained from the aqueous polyvinylpyrrolidone-iodine solutions by removing the water and other volatile constituents, to the use of the aqueous polyvinylpyrrolidone-iodine solutions and of the solid polyvinylpyrrolidone-iodine for producing compositions for disinfection, antisepsis or for wound treatment and for producing wound coverings.

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— *Mit internationalem Recherchenbericht.*
— *Vor Ablauf der für Änderungen der Ansprüche geltenden Frist, Veröffentlichung wird wiederholt, falls Änderungen eintreffen.*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHOD FOR THE PRODUCTION OF POLYVINYLPYRROLIDONE-IODINE IN AN AQUEOUS SOLUTION

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON POLYVINYLPYRROLIDON-IOD IN WÄSSRIGER LÖSUNG

(57) Abstract: The invention relates to a method for the production of iodine polyvinylpyrrolidone in an aqueous solution, whereby an aqueous polyvinylpyrrolidone solution and at least 4.0 wt % of elemental iodine, in relation to the calculated solid content of polyvinylpyrrolidone, are mixed. The said invention is characterized in that at the time of mixing the concentration c of the aqueous polyvinylpyrrolidone solution, in relation to the total amount of polyvinylpyrrolidone and water, and the K-value of polyvinylpyrrolidone, have the following relationship: $c > 100 \times [0.1 + 8: (K + 5)]$ whereby c is given in wt % and the K-value according to Fikentscher ranges from 10 to 100. The invention also relates iodine polyvinylpyrrolidone solutions which are obtained according to said method. Solid iodine polyvinylpyrrolidone can be obtained after removal of water and other volatile components from an iodine polyvinylpyrrolidone solution. The invention further to the use of aqueous iodine polyvinylpyrrolidone solutions containing dissolved solid iodine polyvinylpyrrolidone for the production of disinfectants, weak disinfectants or for the treatment of wounds and for the production of wound coverings.

(57) Zusammenfassung: Gegenstand der vorliegenden Erfindung ist ein Verfahren zur Herstellung von Polyvinylpyrrolidon-Iod in wässriger Lösung, wobei man eine wässrige Polyvinylpyrrolidon-Lösung und wenigstens 4,0 Gew.-% elementares Iod, bezogen auf das als Feststoff gerechnete Polyvinylpyrrolidon, vermischt, dadurch gekennzeichnet, dass zum Zeitpunkt des Vermischens die Konzentration c des wässrigen Polyvinylpyrrolidons, bezogen auf die Gesamtmenge aus Polyvinylpyrrolidon und Wasser, und der K-Wert des Polyvinylpyrrolidons der folgenden Relation gehorcht: $c > 100 \times [0,1 + 8 : (K + 5)]$, wobei c in Gew.-% angegeben ist und der K-Wert nach Fikentscher im Bereich von 10 bis 100 liegt, die Polyvinylpyrrolidon-Iod-Lösungen, die nach diesem Verfahren erhältlich sind, festes Polyvinylpyrrolidon-Iod, das durch Entfernen des Wassers und anderer flüchtiger Bestandteile aus den wässrigen Polyvinylpyrrolidon-Iod-Lösungen erhalten werden kann, die Verwendung der wässrigen Polyvinylpyrrolidon-Iod-Lösungen des festen Polyvinylpyrrolidon-Iods zur Herstellung von Mitteln zur Desinfektion, Feindesinfektion oder zur Wundbehandlung sowie zur Herstellung von Wundauflagen.

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Declaration, Power of Attorney

0050/050733

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for the production of polyvinylpyrrolidone-iodine in an aqueous solution

the specification of which

[X] is attached hereto.

[ ] was filed on _____ as

Application Serial No. _____

and amended on _____.

[x] was filed as PCT international application

Number PCT/EP00/09051

on September 15, 2000

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	**Country**	**Day/Month/Year**	**Priority Claimed**	
19944464.1	*Germany*	*16 September 1999*	[x] Yes	[ ] No

We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**

And we (I) hereby appoint **Messrs. HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number ~~18,495~~; the address of both being Messrs. Keil & Weinkauf, 1101 Connecticut Ave., N.W., Washington, ~~D.C. 20036~~ (telephone ~~202–659–0100~~), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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